DETAILED ACTION

Status of the Claims

Applicants' remarks and amendments filed 8/31/2011 have been entered. Claims 3, 4, 16, 37, and 38 were canceled previously; claims 26-34 are newly canceled. Claims 26 through 34 previously were canceled. Claims 15 and 17-25 remain withdrawn. Claims 1 and 35 stand amended. No new claims were added.

Accordingly, claims 1, 2, 5-14, 35, 36, and 39-48 are under current examination.

Maintained Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5-7, 9-11, 13, 14, 35, 36, 39-41, 44, 45, 47, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seitz, *et al.* (WO 01/89572 A1, published November 29, 2001) in view of Wheatley, *et al.* (WO 02/00149 A1, published January 3, 2002).

The pending claims are directed to a fibrous assembly comprising each a first and second nanofiber, each of which sequesters a first and second reactive component, respectively; the claimed fibrous assembly further specifies release properties.

Regarding claims 1, 6, 7, 10, 11, 14, 35, 40, 41, 44, 45, and 48, the Seitz reference teaches a biocompatible system for generating nitric oxide from sodium nitrite, ascorbic acid, and maleic acid upon treatment with water (see page 4, lines 9-14, 18, and 26-28). The reactants can be sequestered in separate gels that are then admixed or applied as layers to a substrate such as

skin. The reactants are released from gels and are thereby allowed to react to form NO. The reaction rate can be controlled by adjusting the rate of release from the gel. See e.g. page 5, lines 8 to page 6, line 9. For instance, the materials may be combined in a sandwich-like fashion by layering premeasured quantities onto the skin (see page 6, lines 1-6). Alternatively and further regarding claim 35, the reaction components may be converted into aqueous gels prior to combination and reaction (see page 5, lines 1-4). In this case, the second acid gel behaves as a releasing agent since all reactants are dissolved instead of powdered (see page 5, lines 1-4). Regarding claim 13, when prepared as gels, the gelatin macromolecules are associated through dipole-dipole interaction into elongated or threadlike aggregates; the dispersing medium is held in the interstices among the interlacing network of gelatin macromolecules. In this case dissolution medium is preferably aqueous (see page 5, line 29). As such, the interstices meets the limitation of a pore as in claim 5, and the water filling these pores meets the limitation of a fluid in claim 5 and the limitation of a low-molecular-weight liquid as in claims 13 and 47. Thus Seitz taught the concept of sequestering reactants in compartments from which the reactants can be released and allowed to react at a controlled rate in order to form NO.

Regarding claims 1, 2, 5, 36, and 39, Seitz did not teach sequestration of the reactants by nanofibers.

Wheatley teaches polymeric, fiber matrix delivery systems for bioactive compounds (see page 3, lines 28-34). The delivery systems are comprised of polymeric fibers having submicron and/or micron diameters (see page 1, lines 7-

10) wherein the fibers may be arranged as matrices, linear assemblies, or braided or woven structures (see page 6, lines 9-11). Submicron diameter is defined as approximately 1 to 100 nanometers (see page 5, lines 33-35). Wheatley defines the state of the art related to these nanometer sized polymeric fibers in teaching that they can be made by electrospinning (page 3, lines 1-3). These fibers provide methods for modulating the rate of release of a bioactive compound from a delivery system wherein the bioactive compound has been incorporated within or between polymeric fibers (see page 4, lines 7-11). The bioactive agent diffuses, and the time delay can be controlled by varying factors such as polymer diameter and quantity of bioactive agent loaded in the fiber (see page 7, line 29 through page 8, line 2).

Both the Seitz and Wheatley references are directed to combined matrix substrates (i.e., polymeric fibers, layered gels) for the controlled administration of bioactive compounds. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize the polymer fiber substrates as taught by Wheatley in place of the gel substrates taught by Seitz, with a reasonable expectation of success. That is, to use the fiber substrates of Wheatley to release reactants as taught by Seitz, with the reasonable expectation that the released reactants would react, as intended by Seitz. One would have been motivated to do so since Wheatley teaches that these polymeric fiber systems allow controlled modulation of the rate of release of bioactive compounds (see page 4, lines 6-16). Therefore one of ordinary skill

would have understood that the rate of release of reactants could be modulated by adjusting the characteristics of the fibers.

Claims 8 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seitz, *et al.* (WO 01/89572 A1, published November 29, 2001) in view of Wheatley, *et al.* (WO 02/00149 A1, published January 3, 2002) as applied above, and further in view of Santerre et al. (US 5,798,115, patented Aug. 1998).

The teachings of Seitz and Wheatley are delineated above. It is noted that Wheatley teaches that the fibers can be selected from a variety of polymers (see page 6, lines 15-24). Neither of these references teaches the urethane prepolymer and diamine or diol as required in claims 8 and 42.

However, Santerre et al. teach bioresponsive pharmacologically active polymers and articles made therefrom. The invention relates to polymeric compounds and substrates such as implantable medical devices formed from or coated with the pharmacologically active polymeric materials. Pharmacological agents are released in response to in vivo activation at a desired location in a mammal. The pharmacologically active compounds provide in vivo enhanced long term anti-inflammatory, anti-bacterial, anti-microbial, and/or anti-fungal activity (see abstract, in particular). In particular, Santerre et al. teach a diisocyanate (polyurethane prepolymer) reacting with a surface-activated tubing material by reaction of free diisocyanates with active carboxylic acid, amine, or hydroxyl groups (see column 11, lines 25-30). For instance, in Example 4 (see

column 16, lines 20-37), hexamethylene diisocyanate is reacted with Jeffamine-900 polyether diamine following addition of the active agent.

Both Wheatley and Santerre are directed to implantable devices for controllably administering bioactive compounds. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to react the diisocyanate (polyurethane prepolymer) with diamine as taught by Santerre et al. in the polymer devices of Wheatley et al., with a reasonable expectation of success. One would have been motivated to do so since Santerre et al. teach that the pharmacologically active fragment is reacted from a polymeric backbone in *in vivo* applications benefitting from reduced incidence of infection due to the presence of access devices. One further would have been motivated to do so since the *in vivo* pharmacological activity may be for example, anti-inflammatory in nature (see column 6, lines 16-67).

Claims 9 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seitz, *et al.* (WO 01/89572 A1, published November 29, 2001) in view of Wheatley, *et al.* (WO 02/00149 A1, published January 3, 2002) as applied above, and further in view of Anand et al. ("Ion-exchange resins: carrying drug delivery forward", DDT Vol. 6, No. 17, September 2001).

The teachings of Seitz and Wheatley are delineated above. Neither of these references teaches that a reactive component is bound to an ion-exchange resin bead as in pending claims 9 and 43.

However, Anand et al. teach that ion exchange resin beads are comprised of a structural component consisting of a polymer matrix and a functional component to which the counter ion is bound (see page 906, end of first column). Specifically, these beads are applicable to drug delivery systems (see page 908, column 1, paragraph 1).

Both Wheatley and Anand are directed to implantation devices for the administration of bioactive agents. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the ion exchange resin beads as taught by Anand et al. in the polymers for drug delivery as taught by Wheatley et al., with a reasonable expectation of success. One would have been motivated to do so in order to improve the controlled- or sustained- release of drug dosage, particularly since Anand et al. teach that ion exchange resins impart desirable flexibility in designing drug delivery systems since these resins release the drug more uniformly than would a simple matrix (see page 908, column 1, paragraph 2).

Claims 12 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seitz, *et al.* (WO 01/89572 A1, published November 29, 2001) in view of Wheatley, *et al.* (WO 02/00149 A1, published January 3, 2002) as applied above, and further in view of Keefer et al. (US 5,650,447, patented Jul. 1997, submitted in IDS of 1/4/2006).

The teachings of Seitz and Wheatley are delineated above. It is not apparent from these disclosures that one of the fibers necessarily dissolves or

swells in the presence of a releasing agent as required by pending claims 12 and 46.

Keefer et al., however, teach the administration of nitric oxide by release from a polymeric material in order to deliver ameliorating, prophylactic, or therapeutic drug dosing for restenosis and related disorders (see abstract, in particular). Specifically, Keefer et al. explicitly teach that the polymer of the polymer-bound compositions may dissolve in a physiological environment in order to desirably deliver the active agent (see column 9, lines 5-7).

Both Seitz and Keefer are directed to devices for the prophylactic or therapeutic administration of nitric oxide. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to employ the polymer dissolution feature as taught by Keefer et al. in the devices of Seitz, with a reasonable expectation of success. One would have been motivated to do so in order to impart the biodegradable feature as taught by Keefer et al., thereby eliminating the need for fiber removal post delivery of the bioactive agent.

Response to Arguments

Applicants' arguments and request for reconsideration presented 8/31/11 have been fully considered and are summarized and addressed as follows.

Regarding the rejection of claims 1, 2, 5-7, 9-11, 13, 14, 35, 36, 39-41, 44, 45, 47, and 48 under 35 U.S.C. 103(a) over Seitz in view of Wheatley, Applicant presents arguments, especially against claims 1 and 35. Applicant characterizes

the Seitz reference and points out the nitrite and the acid agents are not released from their respective gels and that therefore Seitz does not teach the features of the instantly claimed fibrous assembly. In reply, this position has been fully considered but is not persuasive since one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding the cited combination of Seitz and Wheatley references, Applicant characterizes the Wheatley reference and argues that Wheatley does not teach the features of the instant invention. Applicant then argues, without evidence, that it would not have been obvious to use the polymer fiber substrates as taught by Wheatley in place of the gel substrates as taught by Seitz. Applicant elaborates that because the nitrite and acid in Seitz are not released from the gels, one would not have expected the nitrite and acid to be released from fibers. Applicant then adds the opinion that Wheatley does not relate to the field of the pending claims or the field of Seitz, and asserts that the ordinary artisan would not have had any motivation to combine Wheatley and Seitz. In reply, this position is not persuasive since Wheatley is in fact directed to delivery systems for bioactive compounds, as is the Seitz reference and as are the pending claims; additionally, this position is not persuasive since like the pending claims, Wheatley uses polymeric fibers for the release of actives. As to the relevance of the Wheatley reference, it is underscored that Wheatley teaches polymeric fibers which may be arranged as matrices from which the active

agents are released (see page 6, lines 9-11). Further it is noted that the gel matrices of Seitz perform the same function of holding then releasing active agents. Consequently, it is maintained that the combination of Seitz and Wheatley is proper and would have led to the instant invention, further for the reasons of record. That is, it is maintained that it would have been within the skill of the ordinary artisan to select a carrier for an active agent (or active agent reactant), and that one reasonably would have expected continued success from maintaining a gel carrier/matrix, replacing a gel carrier/matrix with a fiber carrier matrix, or even combining a gel carrier onto a fiber substrate as a carrier.

Regarding the rejections of claims 8 and 42 under 35 U.S.C. 103(a) over Seitz in view of Wheatley and further in view of Santerre, Applicant traverses. Applicant argues that these references are not combinable and concludes that the combination resulting from these references would not be operable. No reasoning or evidence for this position has been presented; therefore, this argument is not persuasive. It is maintained that both Wheatley and Santerre are directed to implantable devices for controllably administering bioactive compounds and that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to react the diisocyanate with diamine as taught by Santerre in the devices of Seitz and Wheatley. One would have been motivated to do so for the reasons of record (see paragraph bridging pages 7 and 8 of rejection mailed 3/1/11).

Regarding the rejections of claims 9 and 43 under 35 U.S.C. 103(a) over Seitz in view of Wheatley and further in view of Anand, Applicant argues that

although Anand teaches using ion exchange resin beads as matrices for drug delivery systems, there is no motivation for combining this teaching with Seitz and Wheatley since Anand also teaches that ion exchange resins might not be optimally applicable to the skin. Applicant characterizes the cited references as being in different technical fields and takes the position that the combination of cited references does not teach the limitations of the pending claims. In reply, Applicant is reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference, rather the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art. In the instant case, the principle of operation of each of the cited references is a structure from which a pharmacologically active agent or agents may be controllably released; as such, it has not been shown how the combination of references allegedly renders the resulting product inoperable for the intended purpose of any of the cited references.

Regarding the rejections of claims 12 and 46 under 35 U.S.C. 103(a) over Seitz in view of Wheatley and Keefer, Applicant argues that "despite Keefer's teaching of a polymer that can dissolve, this reference falls far from teaching or suggesting any of the features of the fibrous assemblies of claims 1 and 35...". In reply, the rejections of claims 1 and 35 have been maintained for the above reasons. Additionally, Applicant argues that “there is simply no evidence as to what the affect would be to replace this gel and then dissolve its replacement. Clearly, Seitz is just no compatible with the Wheatley reference, nor Keefer in

combination with Seitz and Wheatley. Thus, there is no possible combination of Seitz and Wheatley and Keefer that would render claims 12 and 46 obvious" (see page 14 of Remarks, paragraph 4). In reply, the rejections of claims 1 and 35 are maintained for the above reasons, and it is noted that no further reasons against the obviousness rejection of claims 12 and 46 has been presented. Thus, the rejection is maintained for the reasons described above.

Conclusion

No claims are found allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AUDREA BUCKLEY whose telephone

number is (571)270-1336. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on (571) 272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AJB/

/RICHARD SCHNIZER/
Primary Examiner, Art Unit 1635